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# "Implications for Investigator Initiated Trials (IITs)- Risk Based Approaches in Managing Clinical Trials"

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CRCS & CRP Forum, 1st December 2017

# IITs come in all shapes and sizes…

| Phase 1 Trial | Phase 2 Trial | Phase 3 Trial | Phase 4 Study |
|---|---|---|---|
| ▪ Proof Of Concept (POC) Trial<br>▪ Early Clinical Development of new innovative drugs/devices<br>▪ Off-Label use | ▪ Off-Label use (existing rational)<br>▪ New indication<br>▪ New dosing regimen<br>▪ Combination therapy | ▪ Off-Label use (existing rational)<br>▪ New indication<br>▪ New dosing regimen<br>▪ Combination therapy | ▪ Observational studies<br>▪ In-vitro Diagnostics<br>▪ Patient Outcomes Registries<br>▪ Cost Effectiveness Studies<br>▪ Quality Improvement Studies |

**Data from these studies can be used for:**

- ❑ Drug/Device Registration
- ❑ Policy changes (e.g. SOC, Reimbursement, Prescription status)
- ❑ Publication

Volume 14, Number 6 • November/December 2012

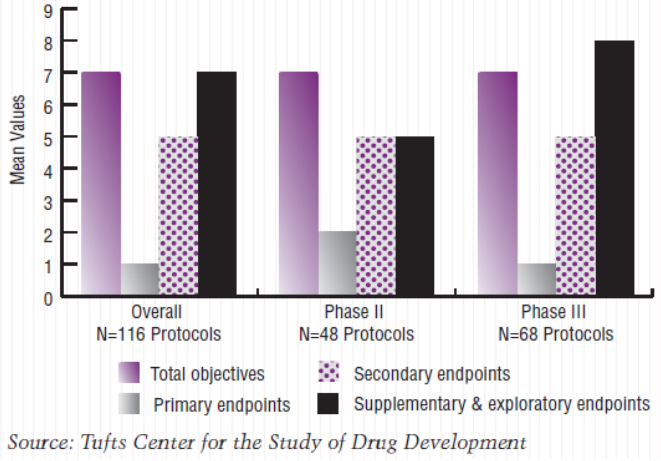
Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Impact REPORT

ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

**The typical clinical trial protocol has an average of 7 objectives and 13 endpoints**

*Protocol: Objectives and Endpoints: 2012*




*Source: Tufts Center for the Study of Drug Development*

Cutting Edge INFORMATION

July 14, 2011 10:02 ET

**Per-Patient Clinical Trial Costs Rise 70% in Three Years**

Volume 16, Number 5 • September/October 2014

Tufts Center for the Study of Drug Development
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Impact REPORT

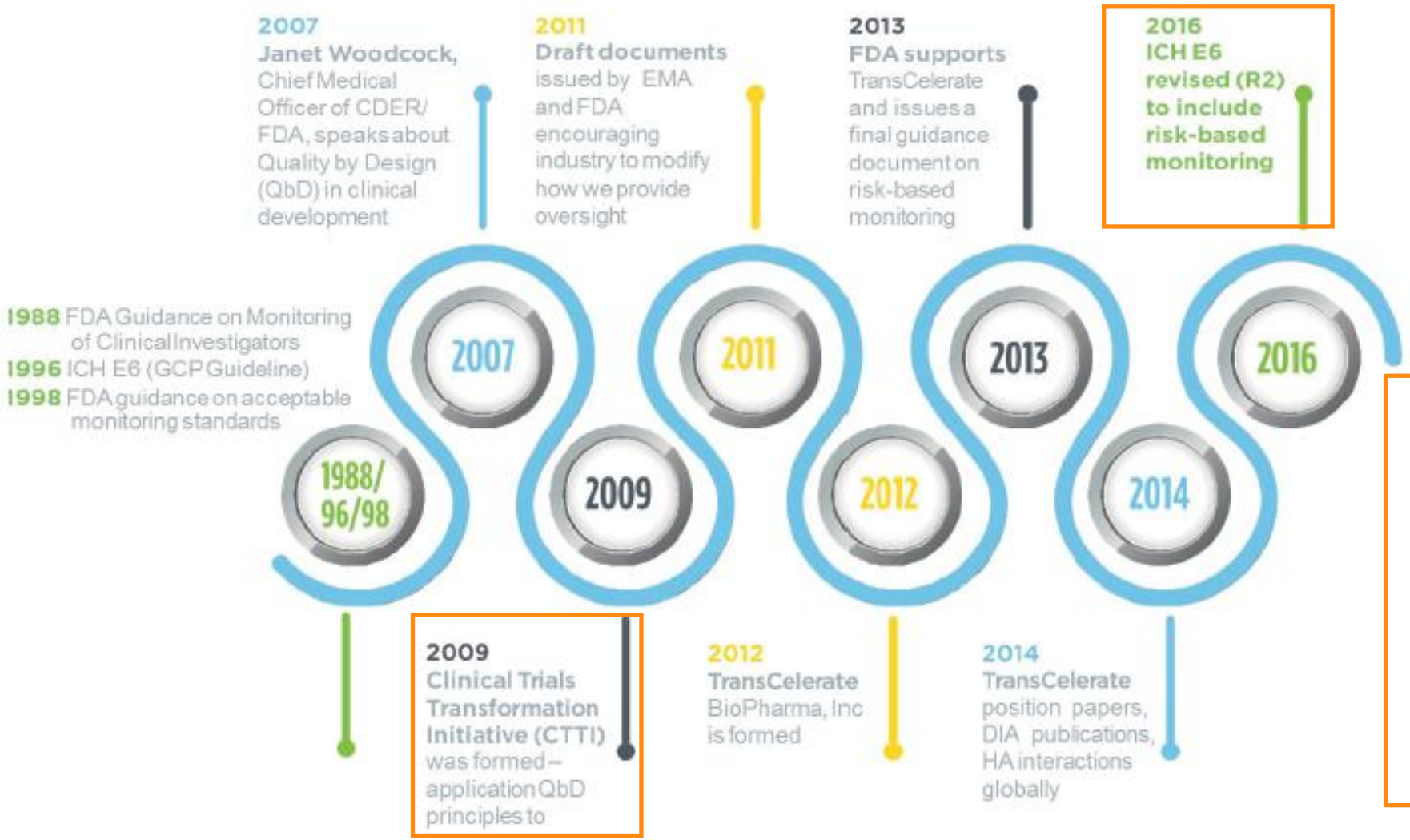
ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

***The incidence of non-core data remains high***

- 21% of procedures in Phase II protocols and nearly one-third of procedures in Phase III protocols collected data that are non-core, i.e., the data do not support primary or key secondary endpoints, regulatory requirements, or standard baseline
- 80% of all Phase II non-core data and 87% of all Phase III non-core data collected were source data verified by study monitors.


.. and we need to customize the strategy to fit the **risk level** and **outcome of the trial/study**

# How has regulatory guidance evolved around ‘risk management’:



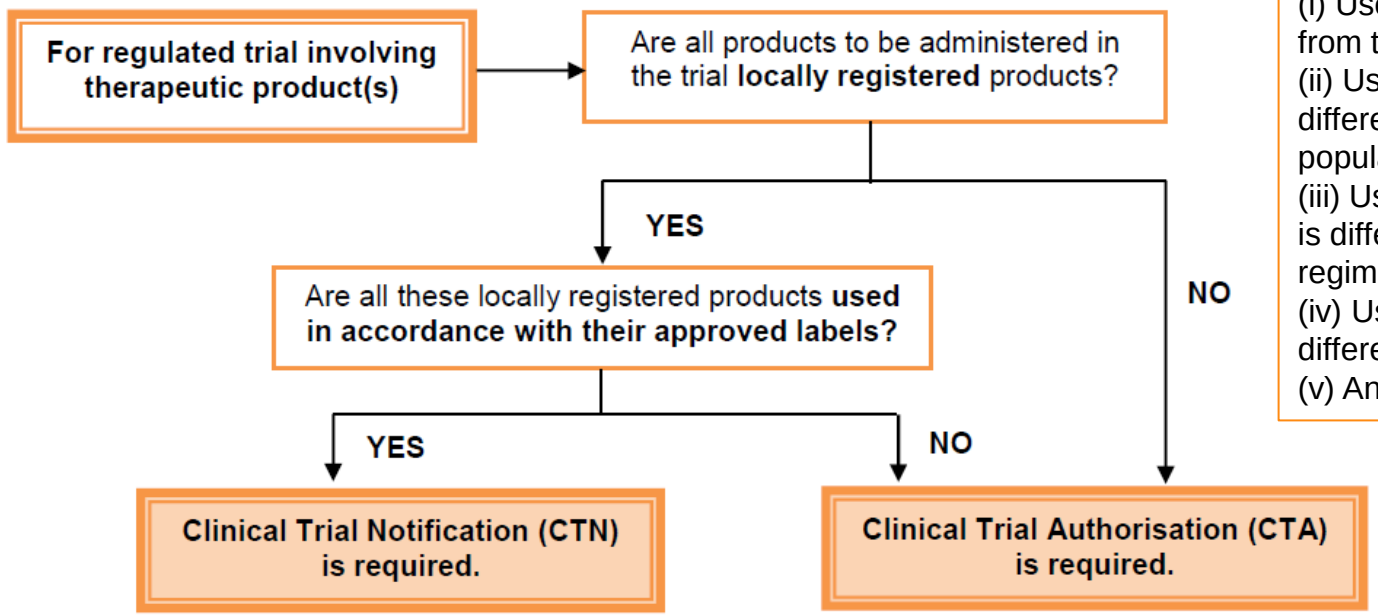

Singapore HSA Regulatory Guidance May 2017: Clinical trials regulated by HSA must comply with the protocol, applicable clinical trials and clinical research material regulations, **ICH E6 (R2) Good Clinical Practice (GCP) Guidelines** and standard operating procedures.

*Reference: BioClinica White Paper 2016: What effect does ICH E6 R2 Have on Risk-Based Monitoring and Overall Quality Risk Management?*
*HSA – Guidance of GCP Inspection Compliance Framework, 2 May 2017*

# How has regulatory guidance evolved around ‘risk management’:

**Singapore HSA Clinical Trials of Therapeutic Products Regulations:**
Under the Health Products Act and the new Health Products (Clinical Trials) Regulations, the existing ‘one-size-fits-all’ Clinical Trial Certificate (CTC) system will be replaced by a risk-based Clinical Trial Authorization-Clinical Trial Notification (CTA-CTN) system.

**Figure 1. CTA or CTN for clinical trials of therapeutic products**




Off Label use:

(i) Use in an indication different from the approved indication(s)
(ii) Use in a patient population different from the approved population(s)
(iii) Use of a dosing regimen that is different from the approved regimen
(iv) Use of a dosage form that is different from the approved form
(v) Any other off-label use

*Reference: HSA Clinical Trial Guidance ISSUED May 2017*

# ICH GCP E6 Addendum (R2) released in November 2016

## Sponsor Responsibilities

**5.0 Quality Management**
Use a risk based approach to quality management:

1. Identify critical processes and data
2. Identify risks to critical trial processes and data
3. Evaluate risks
4. Control risks
5. Communicate risks
6. Review risks
7. Report risks

**How might we apply this to IITs?**

**5.18.3 Nature and Extent of Monitoring**
“The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials. The flexibility in the extent and nature of monitoring is intended to permit varied approaches that improve the effectiveness and efficiency of monitoring. The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring.”

# What are some of the ‘risks’ we might see in an IIT?

## Not enough sites / Investigators accepting the trial

- Local study ‘Sponsorship’
- Indemnity & Insurance challenges
- Drug Reimbursement
- Trial design not good

## Missing out key study procedures

- Trial design not generalized enough to meet standard of care across study sites
- Inadequate resources to perform additional procedures
- Protocol Design too complicated

## Key data not collected for trial subjects

- Case Report Form (CRF) not well designed
- Quality oversight process not in place (clinical monitoring)


## Very low patient accrual

- Inclusion/ Exclusion criteria too restrictive (protocol design issues)
- Drug Reimbursement/ No benefit to patients
- Site Staff unfamiliar with how to identify potential patients
- Inadequate resources to help identify potential patients

## Running out of funds

- Timelines extended
- Budget planning inefficient

# Step 1: Risk Assessment

1. Identify critical processes and data
2. Identify risks to critical trial processes and data
3. Evaluate risks

| Risk Log: |
| --- |
| Whether data for trial will go for Publication or Drug/Device Registration |
| Primary and secondary efficacy endpoints |
| Can the needed sample size be met? |
| Serious Adverse Events– what support in needed? |
| Study population: healthy volunteers or patients or paediatric patients? |
| Is the intervention being used outside its marketing authorisation, e.g. has the dosage regimen/route been modified? If so, what are the implications of any modifications for participants? |
| What are the known/anticipated safety issues and are they all addressed within normal clinical practice (standard care)? |
| Are data being transferred between organisations? Personal data protection being compromised? |
| Is the duration of use compatible with previous experience? |
| Route of drug administration (oral, sub-cutaneuous, intravenous, and if skilled staff is required for administration)? |
| Blinding and unblinding components in study design? |
| Randomization stratification and placebo consideration |
| Might concomitant medications increase the risk, i.e. interactions? |
| For devices, is there a safety impact resulting from the device not being operated properly or failing to operate? |
| Which data points should be monitored and at what frequency? |
| Which data points should be recorded in the Case Report Form? |


Core team identifies Scientific & Operational Risks to drive planning

# Step 1: Risk Assessment

1. Identify critical processes and data
2. Identify risks to critical trial processes and data
3. Evaluate risks

| DEFINING THE RISKS POSED BY ADDITIONAL STUDY PROCEDURES REQUIRED BY THE PROTOCOL WHEN COMPARED WITH STANDARD CARE | | |
|---|---|---|
| Risk | Specify concerns | How will the risks be minimised? |
| | | |

| FOR DRUG/DEVICE TRIALS ONLY: DEFINING PLANS FOR ONGOING SAFETY MONITORING<br>Will a Data Safety Monitoring Board (DSMB) be convened? | | |
|---|---|---|
| Yes ☐ | No ☐ | If no, please justify and describe any alternative plans for the ongoing safety monitoring of the drug/device (e.g. independent data review/medical monitor) |

| PART 3: RISKS TO PARTICIPANTS' RIGHTS | | |
|---|---|---|
| 3a The Consent Process | | |
| Risk | Specify concerns | How will the risks be minimised? |
| | | |

| 3b Protection of Personal Data | | |
|---|---|---|
| Risk | Specify concerns | How will the risks be minimised? |
| | | |

| PART 4: RISK TO DATA INTEGRITY | | |
|---|---|---|
| Risk | Specify concerns | How will the risks be minimised? |
| | | |

Investigator's signature: _____ Date: _____

| OVERALL RISK CATEGORY FOR THE TRIAL | |
|---|---|
| **Drug/Device Clinical Trials** | **Risk Category** |
| Trials involving a drug entered onto the Australian Register of Therapeutic Goods (ARTG) if:<br>- They relate to the licensed range of indications, dosages and forms, or;<br>- They involve off-label use, if this off-label use is established practice and supported by sufficient published evidence and/or guidelines (for example in paediatrics or oncology).<br>Trials involving a medical device used within its product indications if knowledge derived from controlled trials already exists. | ☐ **TYPE A** Risk comparable to standard medical care |
| 1) Trials involving a drug entered onto the ARTG if:<br>- Such products are used for a new indication (different patient population/disease group) or;<br>- Substantial dosage modifications are made or;<br>- They are used in combinations for which interactions are suspected.<br>2) Trials involving a drug **NOT** entered onto the ARTG if:<br>- The active substance is part of a drug that is entered onto the ARTG.<br>3) Trials involving a medical device used:<br>- Outside the scope of certification or;<br>- Within the scope of certification, but no knowledge from controlled trials exists. | ☐ **TYPE B** Risk somewhat higher than standard medical care |
| 1) Trials involving a drug not entered onto the ARTG.<br>2) Trials involving a medical device not entered onto the ARTG.<br>N.B. A grading other than 'TYPE C' may be justified if there is extensive class data or pre-clinical and clinical evidence. | ☐ **TYPE C** Risk markedly higher than standard medical care |

*Reference: NSWH Risk-guidance for Investigator-led research*

# Step 1: Risk Assessment

1. Identify critical processes and data
2. Identify risks to critical trial processes and data
3. Evaluate risks

Singapore HSA Clinical Trial Guidance Issued May 2017

**4.1. Healthy volunteer trials**
All healthy volunteer trials, which involve locally registered therapeutic products will require a CTA, unless the products are used in accordance with approved labels **and** the approved population in the terms of product registration is healthy individuals (e.g. vaccine given usually to healthy individuals).

| Risk Log: |
| --- |
| Whether data for trial will go for Publication or Drug/Device Registration |
| Primary and secondary efficacy endpoints |
| Can the needed sample size be met? |
| Serious Adverse Events– what support in needed? |
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Singapore HSA Clinical Trial Guidance Issued May 2017

**4.2. Placebo-controlled clinical trials**
While placebo comparator is usually an unregistered product, the inert nature of the placebo renders the use of an unregistered placebo to be of “low risk” in comparison to the use of an unregistered therapeutic product. Therefore, a trial on a registered product (within label) with an unregistered placebo will be subject to the regulatory requirements for a CTN (instead of a CTA).

# Step 2: Risk Management

4. Control risks
5. Communicate risks
6. Review risks
7. Report risks

**5.0.4 Risk Control**

The sponsor should decide **which risks to reduce and/or which risks to accept.**

Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedures, and training in processes and procedures.

Items that should be 100% source-verified during on-site monitoring visits

| | Academic/ Govt/ Coop. Group (%) |
|---|---|
| **Consent** | **100%** |
| **Serious Adverse Event report** | **75%** |
| **Primary End-points report** | **62%** |
| Eligibility criteria | **46%** |
| Non-serious adverse event reports | **23%** |
| Secondary End-points report | **15%** |

| Above 80 | 50-79 | Below 49 |
|---|---|---|

The question read: Does your organization verify CRF data vs source data (source data are contained in source documents; e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, X-rays)

*Adapted from Morrison et al Monitoring the quality of conduct of clinical trials: a survey of current practices. Clinical Trials 2011; 8: 342–349.*

# Step 2: Risk Management

4. Control risks
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**5.18.7 Monitoring Plan**
The sponsor should develop a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial.

The plan should describe the monitoring strategy, the monitoring responsibilities of all the parties involved, the various monitoring methods to be used, and the rationale for their use

Examples:

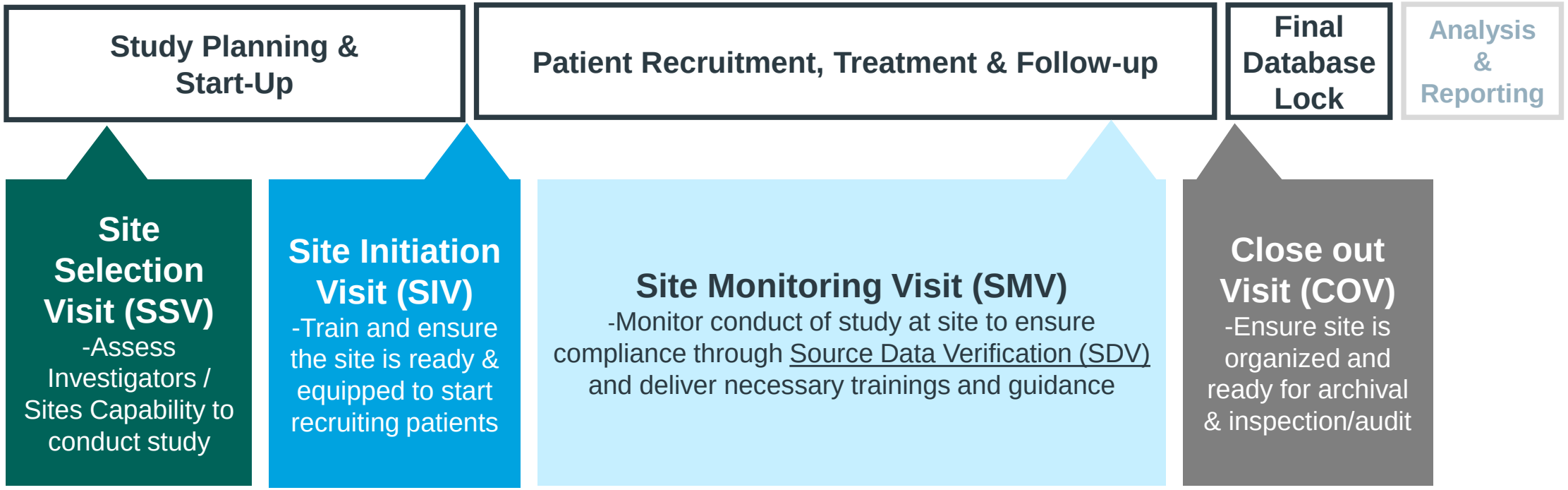
| | Low Risk (L) | Medium Risk (M) | High Risk (H) |
|---|---|---|---|
| **Initiation/ Training** | Telephonic OR On-site | On-site | On-site |
| **Monitoring Method** | On-Site Annually + Remote Monitoring | On-Site every 6 months + Remote Monitoring | On-Site every 2-4 months + Remote Monitoring |
| **Source Data Verification % (SDV)** | 10-20% | 25-50% | 50-100% |
| **Close-Out** | Telephonic or On-site | Telephonic or On-site | On-site |
| **Ad-Hoc (Quality Issue)** | 1 per site | 1 per site | NA |

Telephonic SIV
Annual Monitoring visits

On-Site SIV
Quarterly Monitoring Visits

3 On-Site SIVs per site
Monitoring visits every 2 months

# Difference types of on- site monitoring visits & training opportunities:

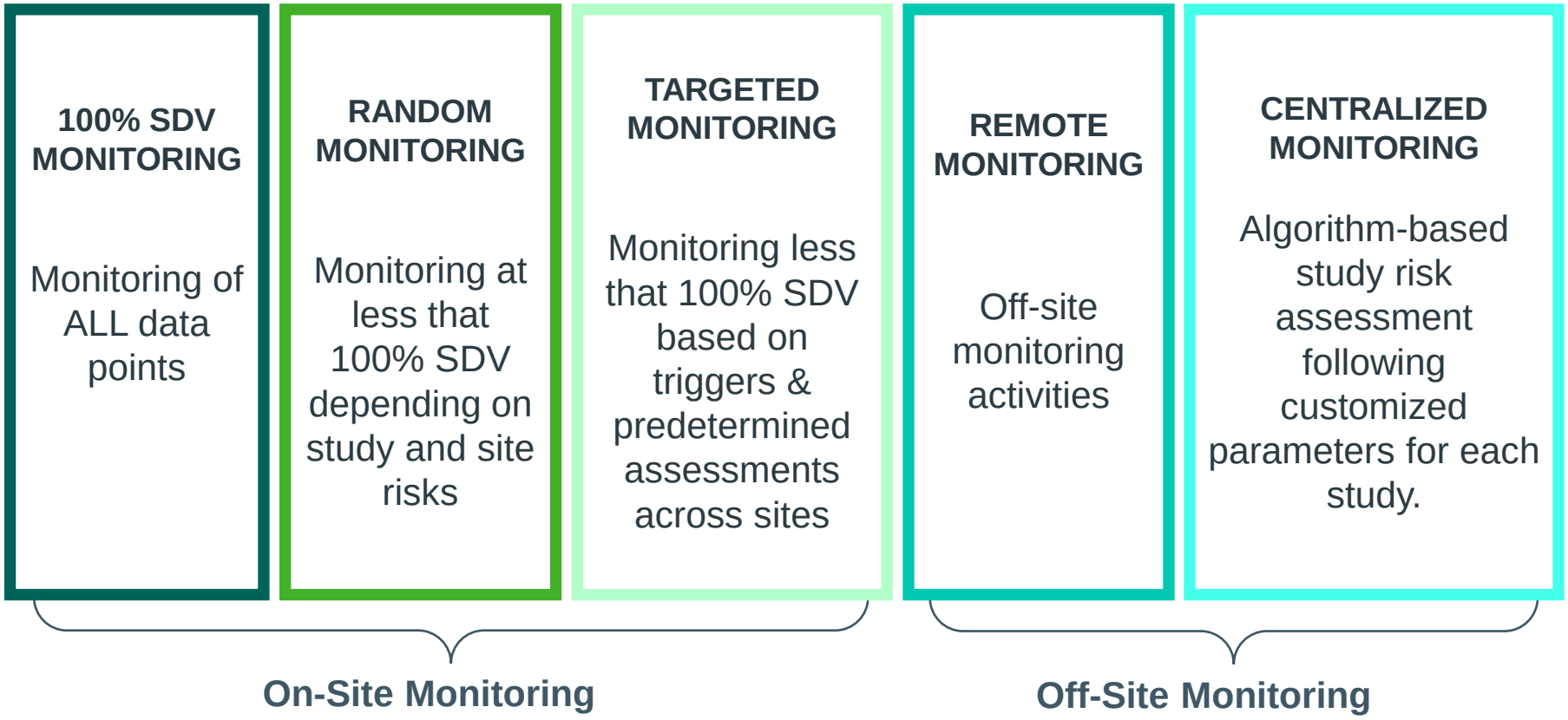



- ✓ Inadequate resources to help identify potential patients
- ✓ SOC versus trial design

- ✓ Site Staff unfamiliar with how to identify potential patients
- ✓ Protocol Design too complicated

- ✓ Quality oversight process
- ✓ Inadequate resources to perform additional procedures/ identify patients
- ✓ Protocol Design too complicated/ data not being entered

# 5 Monitoring Methods:




"Source data verification (SDV), a verification of the conformity of the data presented in case report forms with source data, is conducted to ensure that the data collected is reliable and allows reconstruction and evaluation of the trial"

*Reference US FDA: Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring 2013 & EMA ICH harmonised tripartite guideline E6: (PMP/ICH/135/95).2011*

# A Tool for CRAs to aid more focused monitoring…

A Source Document Verification plan signed off by all stakeholders to ensure focus and consistency in oversight delivery

| | On-Site Monitoring | Remote Monitoring | Completed for All subjects | Completed only for first 5% of patients |
|---|---|---|---|---|
| ***Subject/Patient documentation:*** | | | | |
| Review of Informed Consent Forms (ICFs) | | | | |
| Subject eligibility verification | | | | |
| Primary End-point data verification | | | | |
| Secondary & Tertiary End-point data verification | | | | |
| Adverse Event documentation review | | | | |
| Review of SAE's reported | | | | |
| Drug dosing and administration review | | | | |
| Lab sample documentation review | | | | |
| | | | | |
| ***Investigational product (IP)/ Drug Management*** | | | | |
| Drug Storage and Accountability logs | | | | |
| Accountability check at Pharmacy if needed | | | | |
| Drug shipments to site tracking logs | | | | |

**ICH GCP ADDENDUM November 2016**
*5.18.7 Monitoring Plan*

**The plan should also emphasize the monitoring of critical data and processes**. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training.

# Step 2: Risk Management

**5.18.3 Extent and Nature of Monitoring**

Centralized monitoring processes provide additional monitoring capabilities that can complement & reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data.

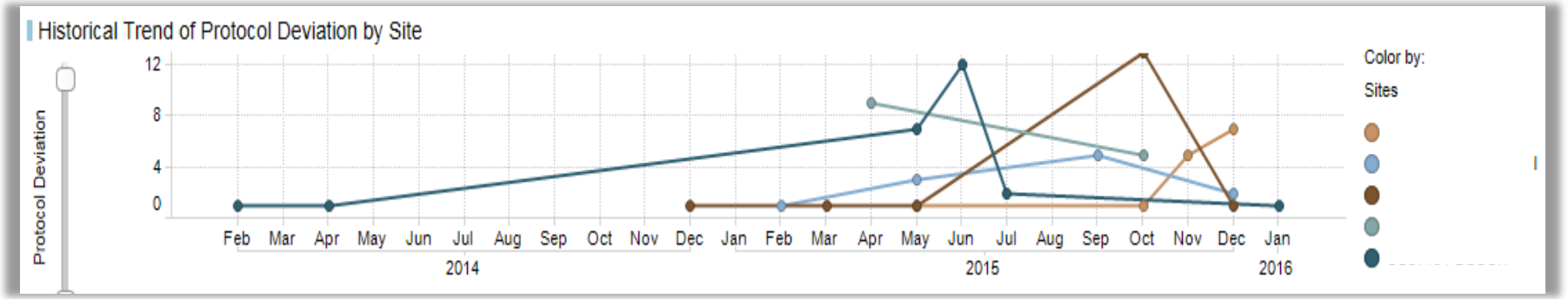
Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:
(a) identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.
(b) examine data trends such as the range, consistency, and variability of data within and across sites.

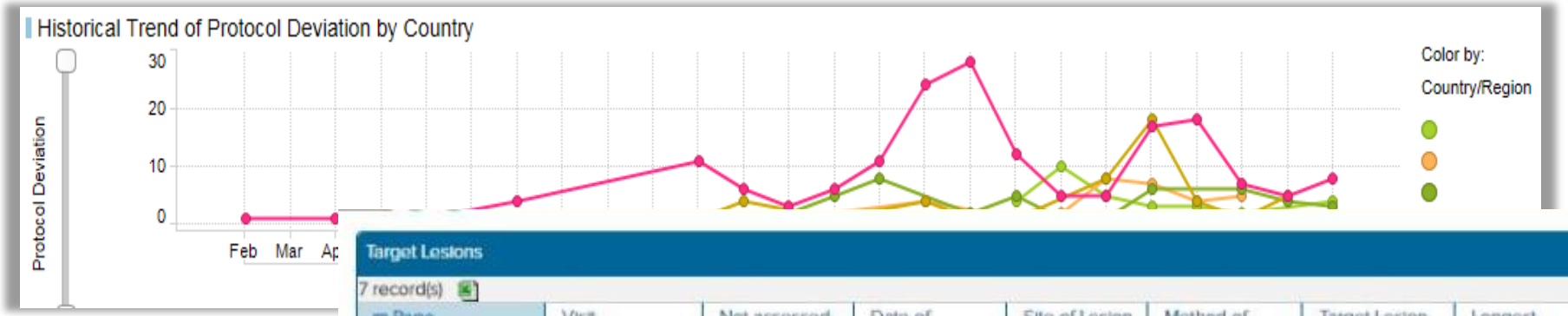
Factors that would trigger an on-site monitoring visit:

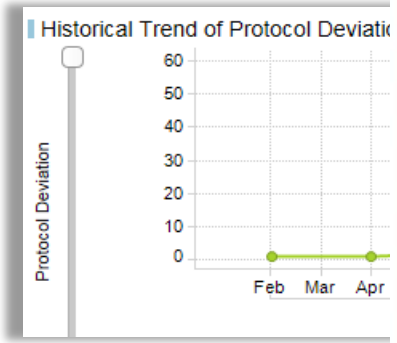
| | All types of organizations (%) |
|---|---|
| **# of Protocol Deviations** | **86-100%** |
| **Suspected fraud** | **80-100%** |
| Rate of Enrollment | 60-89% |
| Missing CRFs | 64-89% |
| **Lab data signals** | |
| **Incidence of AEs** | |
| Geographic location of site | |
| Lack of experience of site | |
| No of Data queries | |

| Range 100-80 | Range 60-89 | Below 60 |
|---|---|---|

*Adapted from Morrison et al Monitoring the quality of conduct of clinical trials: a survey of current practices. Clinical Trials 2011; 8: 342–349.*




**High-end Analytics support**

**Simple Analytics support**

**Target Lesions**

7 record(s)

| Page | Visit | Not assessed | Date of Evaluation | Site of Lesion | Method of Evaluation | Target Lesion Response | Longest Diameter | Status | Total Queries | Open Queries | Page Links | Page Attachments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Target Lesions (1) | Screening Visit - Chemotherapy | | 28-JUL-2017 | Lungs | MRI | Complete Response | 10 | | 22 | 0 | 0 | 0 |
| Target Lesions (2) | Screening Visit - Chemotherapy | X | | | | | | | 3 | 0 | 0 | 0 |
| Target Lesions (3) | Screening Visit - Chemotherapy | | 03-AUG-2017 | | | | | | 28 | 1 | 0 | 0 |
| Target Lesions (4) | Screening Visit - Chemotherapy | | | | | | 10 | | 26 | 25 | 0 | 0 |
| Target Lesions (5) | Screening Visit - Chemotherapy | | | | | | 10.1 | | 27 | 22 | 0 | 0 |
| Target Lesions (6) | | | | | | | 15 | | 22 | 22 | 0 | 0 |
| Target Lesions (7) | | | | Lung | | | 10 | | 23 | 14 | 0 | 0 |

Add

# Some challenges with Risk-Based Monitoring (RBM):

- Different regulations in participating countries (e.g. 100% SDV in China per CFDA requirement)
- Lack of effective identification of key risk indicators/parameters and issues
- Continuous training to monitors and site staff to boost understanding on RBM model
- Difference in visit frequency between sites results in disparity between SDV and non SDV content. SDV content is reviewed on priority, leaving non SDV content to be reviewed on the next visit. (snowball effect)
- Less motivation for sites to recruit when the Monitor is not onsite.

**Critical to monitor IITs:**

Limited time
Limited study funding & resources
Limited experience
Limited/no site selection/evaluation process
Limited SOPs/guidance at the site

*Catherine's study team had changed so many times, she'd done more staff inductions than site initiations!*

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IMS Health & Quintiles are now

IQVIA™

# Thank You